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10/511,455	08/29/2005	Benjamin Simon Pickard	9013.63	2347

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,455	PICKARD ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/20/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-41 and 46-55* is/are pending in the application.

4a) Of the above claim(s) *49-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-41 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 38-41 and 46-55 are pending.

Claims 49-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/20/2007.

Claims 38-41, and 46-48 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of the invention of Group 3 (claims drawn to methods of diagnosing schizophrenia) in the reply filed on 12/20/2007 is acknowledged. Applicant's further election with traverse of the gene GRIK4, is also acknowledged. The traversal is on the ground(s) that all of the instantly presented claims depend from claim 38 and thus have unity of invention with the special technical feature being a method of diagnosing schizophrenia and/or affective psychosis or susceptibility to schizophrenia and/or affective psychosis in an individual wherein the methods comprises determining if the *GRIK4 g*ene in the individual has been disrupted by a mutation of chromosomal rearrangement. This is not found persuasive because the recitation of additional genes in claims 49-55 is a recitation of different requirements in a Markush-type format. According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(A) and Section (f)(i)(B)(1) of Annex B of the PCT Administrative instructions, all alternatives of a Markush group must have a common property or activity and a common structure. The nucleic acid sequences of the genes and their expression products in the abovementioned claims each have a different chemical structure and do not share a

common structure. Furthermore, the nucleic acid sequences do not share a common property or activity in that, as addressed in this Office Action, there is not an enabled asserted common property of being indicative of schizophrenia and/or affective psychosis. Furthermore, the active method step of the independent claim (i.e. claim 38) of determining if the *GRIK4* gene in the individual has been disrupted by a mutation of a chromosomal rearrangement, is not a special technical feature as it was known in the prior art, as evidenced by the art rejections presented in this Office Action. Upon election of any group that contains any of the aforementioned claims, Applicant is required to elect one of the members of the group set forth in the claim.

2. As such, with Applicant's election of the gene *GRIK4*, claims 38-41 and 46-48 are examined on the merits, and claims 49-55 are withdrawn from examination as to a non-elected invention, where claims 49-55 specifically require non-elected genes.

The requirement is still deemed proper and is therefore made FINAL.

Objection to the Specification - Sequence Compliance

3. This application (10/511,455) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below:

> The specification contains numerous presentations of nucleic acid sequences that are not identified by any SEQ ID NO. See for example pages 31-34, 38, 39, and 43.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must and amend the specification to include the appropriate SEQ ID NOs from the sequence listing.

In order for any response to this Office Action to be considered fully responsive, the response must put the application in compliance with the sequence rules.

Drawings

4. The drawings are objected to because:

> The drawings provide nucleic acid and amino acid sequences that are not identified by any SEQ ID NO in either the drawing or the descriptions of the drawings (p.21-26). Additionally, there are drawings that span multiple pages, where the second and subsequent pages do not properly identify the drawing. For example, pages 3-5 of the drawings appear to encompass 'Figure 3', however pages 4 and 5 of the drawings are not labeled to idnetify, for example, 'Figure 3, continued'.

5. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering

of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either “Replacement Sheet” or “New Sheet” pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Objection to the Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example pages 27, 28, 29, and 45. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

7. The disclosure is objected to because of the following informalities:

Page 35 of the specification recites the term ‘comorbin schizophrenia’, where likely the phrase ‘comorbid schizophrenia’ is intended.

Appropriate correction is required.

Information Disclosure Statement

8. The listing of references on pages 49-56 in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be

submitted in a separate paper." Therefore, unless the references on pages 49-56 have been cited by the examiner on form PTO-892, or provided on an IDS consistent with 37 CFR 1.98(b), they have not been considered.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 38-41 and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are unclear over recitation of the purpose of the claimed method as a method 'of diagnosing schizophrenia and/or affective psychosis or susceptibility to schizophrenia and/or affective psychosis in an individual', as recited in claim 1. The claimed methods require only the single active method step of 'determining if the GRIK4 gene in the individual has been disrupted by a mutation or chromosomal rearrangement'. However the step of 'determining' is not 'diagnosing', and thus there is not a nexus between the purpose of the method as stated in the preamble of the claim and the single required method step. It is thus unclear how the single method step accomplishes the recited purpose of the claimed method. The claims may be made more clear by including a positive process step in which the results of the 'determining' step are correlated with the diagnosis of schizophrenia and/or affective psychosis or susceptibility to schizophrenia and/or affective psychosis in an individual.

Claim Rejections - 35 USC § 112 1st ¶ - Enablement

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 38-41 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

Claims 38-41 and 46-48 are drawn to a method of diagnosing schizophrenia and/or affective psychosis, or susceptibility to the same. The claimed methods requiring determining if the GRIK4 gene in an individual is disrupted.

The claims encompass methods for determining disruption by detecting mRNA level (claim 39), detecting gene product by immunological techniques (claims 40 and 41), and nucleic acid hybridization techniques (claims 46-48).

The claims encompass the determination of any mutation or chromosomal rearrangement.

The claims encompass the analysis of any subject organism.

The nature of the invention thus requires knowledge of a correlation between any mutation of chromosomal rearrangement that disrupts the GRIK4 gene and the presence of or susceptibility to schizophrenia and/or affective psychosis.

Direction provided by the specification and working example

The instant specification (p.17) asserts that the presence of or susceptibility to schizophrenia and/or affective psychosis may be determined by determining if GRIK4 has been disrupted in an individual. The specification provides, relevant to the analysis of the GRIK4 gene, an example (p.33 – Example 3) of a single particular patient (i.e. patient 2). The specification indicates that patient 2 suffered from chronic schizophrenia, and had complex chromosome abnormalities (p.34). The specification teaches analysis of a particular chromosome breakpoints on chromosomes 2 and 11, and the detection of an 11q23.3 breakpoint using cosmid FISH.

The instant specification does not provide any guidance or examples regarding relative mRNA levels as indicative of any particular chromosome rearrangement.

The instant specification does not provide any guidance or examples regarding immunological methods to detect a gene product that is indicative of any particular chromosome rearrangement.

The instant specification provides only an example of a single human subject, and does not provide any examples of any non-human subjects, nor provide any validation of the proposed correlation between a chromosomal rearrangement and schizophrenia by analysis of any family pedigrees or any other separate populations in which the association is confirmed.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to making determining if a particular gene sequence has an alteration is high, the level of unpredictability in correlating any detected nucleic acid sequence mutation with a particular diagnosis, such as schizophrenia or any affective psychosis, is higher. Such unpredictability is demonstrated by the prior art and the post-filing art.

Because the claims encompass any subject organism it is relevant to point out the unpredictability in extrapolating results regarding any asserted association of a gene mutation with a phenotype in humans to any other organism. Similar nucleotide sequences may encode polypeptides with markedly different functionalities. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S).

Because the claims encompass determining if GRIK4 has been disrupted by detecting relative level of mRNA expressed by the gene, or detecting GRIK4 gene products by an immunological techniques, while the specification teaches only detection of GRIK4 mutations using sequence specific hybridization, it is relevant to point out the unpredictability in detecting a gene mutation using relative level of mRNA expressed by the gene or immunological techniques. Regarding relative mRNA levels, Orntoft et al (2002) teaches that mRNA expression and gene copy alteration are unpredictably discordant (Table I; p.40 left col.). It is thus unpredictable, given the lack of any evidence in the instant specification, as to what level of GRIK4 mRNA expression, as

compared to any particular standard control, would be indicative of any GRIK4 disruption. Additionally, the claims encompass analyzing the level of GRIK4 gene product using immunological techniques, however the post-filing art of Chan teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus it is unpredictable as to whether or not any detection of GRIK4 gene product level would be indicative of the particular disruption that is taught in the instant specification.

Furthermore, while the claims encompass any GRIK4 disruption cause by any mutation or rearrangement (i.e. any amount of nucleotide sequence alteration), it is relevant to point out that the instant specification teaches only a single particular chromosomal rearrangement. And while the specification hypothesizes (p.35) that reduced GRIK4 gene dosage resulting from GRIK4 disruption is the cause of the schizophrenic phenotype in patient 2, the specification provides no evidence in support of this proposed mechanism. There is no analysis of any functional consequences of the GRIK4 rearrangement. The breadth of mutations encompassed by the broad language of the claims is particularly relevant considering the post-filing art of Li et al and Shibata et al, which indicate a lack of association between GRIK4 SNPs and schizophrenia in Chinese and Japanese populations, respectively.

It is also relevant to point out that the asserted association between GRIK4 mutations and schizophrenia is based on the analysis of a single patient. Lucentini (2004) teaches the general unpredictability in associating a gene or mutation of a gene

with a particular phenotype. Lucentini reveals that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). For example, in an anlysis of a translocation involving locus 11q23 (where the GRIK4 gene is at 11q23.3), Baysal et al (2002) teaches that in a family the particular translocation only partially cosegregates with the bipolar phenotype, with 5 translocation carrier not being affected.

Finally, because the claims encompass associating any GRIK4 mutation with a diagnosis or susceptibility to any affective psychosis, where the specification teaches only the analysis of a single patient with schizophrenia, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to perform large case:control and family studies to determine that the GRIK4 gene is robustly and reliably associated with schizophrenia or any other affective psychosis. Such experimentation would require the analysis of any mutation in the GRIK4 gene, any further require the analysis of any subject organism, including any non-human subjects. One would also be required to establish that mRNA or gene product levels are indicative of any GRIK4 mutation.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Claim Rejections - 35 USC § 102

It is noted that the claims of the instant application have been rejected under 35 USC 112 1st ¶ for lack of adequate written description and lack of enablement in part because of the recitation of the intended use of the claimed products. However it is noted that the teachings of the applied prior art, while anticipating the structural limitations of the broadest reasonable interpretation of the claimed products, do not serve to provide an adequate written description or enablement of the claimed subject matter in view of the prior art.

Furthermore, it is noted that the preambles of the claims and the recitations of the intended use of the claimed products are not given weight when comparing the

required structural limitations of the claimed products to those taught by the prior art. As noted in the MPEP 2111.02:

> A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.

Further, in Pitney Bowes Inc. v. Hewlett-Packard Co., 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.

Thus, in the instant case, recitations of the intended use of the claimed products are not given limiting weight in determining the patentability of the claimed products. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by Gurling et al (2001).

Relevant to claim 38, Gurling et al teaches an analysis of human chromsome 11, including an analysis of the microsatellite marker D11S925. Because the marker D11S925 is contained within the GRIK4 gene (as disclosed in the instant specification,

p.37 ln.35 - p.38 ln.1), the analysis of Gurling et al is determining if the GRIK4 gene in an individual has been disrupted by a mutation.

15. Claims 38 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Szpirer et al (1994).

Szpirer et al teaches the chromosomal localization of the GRIK4 gene in humans.

Relevant to claims 38 and 46-48, Szpirer et al teaches *FISH* analysis of the human GRIK4 gene (p.11850 - In situ hybridization), which is determining if the GRIK4 gene in an individual has been disrupted by a chromosomal rearrangement).

Relevant to claims 46-48, Szpirer et al teaches GRIK4 analysis using *FISH* (where absent any limiting definition or required steps for 'high-throughput' *FISH*, the teachings of Szpirer et al satisfy the required limitations of claim 46), which includes the use of labeled oligonucleotides (claims 47 and 48) *(*p.11850 – Southern blot analysis and hybridization probes, In situ hybridization; p.11851 – Subchromosomal localization of the human GRIK4 and GRIK5 genes by fluorescence in situ hybridization (FISH)).

Conclusion

16. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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